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MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
BHAT, NARAYAN KAMESHWAR	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,803	GAO ET AL.	
	Examiner	Art Unit	
	Narayan K. Bhat	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,9,22,24,26,28,30,31,37,41-43,46,47,49,53,57-61 and 65-76* is/are pending in the application.

4a) Of the above claim(s) *65-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,9,22,24,26,28,30,31,37,41-43,46,47,49,53 and 57-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/06/2006, 4/26/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Acknowledgment is made of applicant's claim for foreign priority based on an application filed on June 30, 2006. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

2. Applicant's election without traverse of Group I invention in the reply filed on October 30, 2007 is acknowledged.

3. Claims 1-4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 47, 49, 53, 57-61 and 65-76 are pending in this application.

4. Claims 65-76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention of group II there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 30, 2007.

5. Claims 1-4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 47, 49, 53 and 57-61 are under prosecution.

Amendments to the Claims

6. Amendments to claims 2-4, 37 and 60 have been reviewed and entered.

Specification

7. The specification disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

Specifically the application fails to comply with CFR 1.821(d), which states:

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The specification discloses nucleotide sequences in the instant specification, in Table 1, by probe name (Pg. 37- 43) but do not list corresponding SEQ ID NO in Table 1, which can be identified with the SEQ ID numbers submitted in a computer readable format to the USPTO. For compliance with sequence rules, it is necessary to include the SEQ ID numbers wherever the sequence appears in the specification (see MPEP 2422.03 for further guidance).

For any response to this office action to be complete, applicants are required to carefully review the entire specification for any nucleic acid/ amino acid sequences and list them in a sequence listing and identify them with sequence identifier. Appropriate correction is required.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3-4, 9, 22, 24, 28, 30-31, 37, 49, 53 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Apple et al (USPN 5, 567,809 issued Oct. 22, 1996).

Regarding claim 1, Apple et al teaches a method of HLA DR beta DNA (DRB) typing, the method includes preparing the target nucleic acids from cell lines (Example 7, column 41, lines 23-27), i.e., isolating a target cell comprising a target gene from a suitable sample and obtaining a preparation comprising a target nucleotide sequence that is at least a part of said target gene from said isolated target cell (column 41, lines 25-33) and further teaches using genomic DNA that contains other genes not related to HLA DR beta.

Apple et al also teaches a reverse dot blot, i.e., a chip comprising a membrane support suitable for use in nucleic acid hybridization having immobilized thereon an oligonucleotide probe complementary to DRB target nucleotide sequence (Example 8, column 43, lines 35-60) and further teaches that the chip contains probes specific for particular allele type and additionally contains a control probe that detects all of the alleles (columns 53, 54 and 56, lines 50-67, 15-30 and 33-41). The control probe of

Apple et al is the positive control probe as defined in the instant specification (paragraph 0027) and also because it detects all of the DRB alleles (column 56, lines 33-41).

Apple et al further teaches hybridizing the array and assessing hybridization between said target nucleotide sequence and/or said another nucleotide sequence and said probes comprised on said chip to determine the type of DRB target gene (Figs 10-13, column 56, lines 42-48).

Regarding claim 3, Apple et al teaches that the target gene is DR beta DNA (DRB), i.e., human leukocyte antigen HLA (column 3, lines 51-60)

Regarding claim 4, Apple et al teaches that the suitable sample is a human bladder tissue that comprises human nucleic acid (column 42, lines 46-54).

Regarding claim 9, Apple et al teaches that the preparation of the target nucleotide sequence comprises a nucleic acid amplification step (column 3, lines 62-65).

Regarding claim 22, Apple et al teaches that the target nucleotide sequence is amplified by PCR using biotinylated primer for hybridization and detection by SA-HRP (column 43, lines 40-48) thus teaching DNA is single stranded at the time of hybridization.

Regarding claim 24, Apple et al teaches that a labeled biotinylated target nucleotide sequence is obtained (column 43, lines 40-48).

Regarding claim 28, Apple et al teaches that the probes are tiled with poly dT to attach the probe to the membrane, thus teaching probe comprised on the chip are modified (Column 43, lines 54-60).

Regarding claim 30, Apple et al teaches 22 different DRB probes fixed on the membrane, i.e., chip that meets the limitation of the chip comprises 1-400 different types of probes (Examples 8 and 9, columns 53 and 54 and lines 50-67 and 15-38).

Regarding claim 31, Apple et al teaches two panels of probes containing 11 different DRB probes fixed on the membrane, i.e., chip and further teaches one panel for hybridizing with the DRB amplification products (Example 9, column 53, lines 51-67) and the other with the DRB1-specific amplification products (Example 9, column 54, lines 15-38) thus teaching multiple arrays of probes and each array comprises 11 probes that meets the limitation of each array comprises 1-400 different types of probes.

Regarding claim 37, Apple et al teaches that 5 to 10 picomoles of the probes, i.e., multiple copies of a probe is immobilized on the chip (column 44, lines 31-35).

Regarding claim 49, Apple et al teaches hybridization solution comprises SSPE and SDS, i.e., surfactant (column 44, lines 52-55).

Regarding claim 53, Apple et al teaches that the hybridization reaction is conducted at a temperature of 50 C which is about 42.C to about 70C (column 44, line 52).

Regarding claim 61, Apple et al teaches that the oligonucleotide probe is complementary to a target HLA gene (column 53, lines 18-25).

10. Claims 1-2, 4, 9, 22, 24, 26, 41, 43, 49 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Straus (USPGPUB NO. 2002/0086289 published July 4, 2002).

Regarding claim 1, Straus teaches a method for genomic profiling, the method includes obtaining samples, enriching cells and lysing cells and fixing the DNA on to a solid support (Fig. 5, paragraphs 206-208) thus teaching isolating a target cell comprising a target gene from a suitable sample and obtaining a preparation comprising a target nucleotide sequence that is at least a part of said target gene from said isolated target cell. Straus also teaches adding positive control DNA samples not related to test DNA samples thus teaching another nucleotide sequences not related to said target genes (paragraph 210).

Straus also teaches a detection array, i.e., a chip comprising a support suitable for use in nucleic acid hybridization having immobilized thereon an oligonucleotide probe complementary to said target nucleotide sequence (Fig. 5, paragraph 215) and further teaches that the array also contain at least one of the following oligonucleotide control probes: a positive control probe, a negative control probe, a hybridization control probe (paragraph 215).

Straus further teaches hybridizing the array and assessing hybridization between said target nucleotide sequence and/or said another nucleotide sequence and said probes comprised on said chip to determine the type of said target gene (paragraphs 230-235).

Regarding claim 2, Straus teaches that target sample is blood that contain leukocytes (paragraph 200).

Regarding claim 4, Straus teaches that the suitable sample is human body fluid sample that includes blood, sputum, cerebrospinal fluid, sputum and feces, that comprises human nucleic acid (paragraph 154).

Regarding claim 9, Straus teaches that the preparation of the target nucleotide sequence comprises a nucleic acid amplification step (Fig. 5, paragraph 211).

Regarding claim 22, Straus et al teaches that the target nucleotide sequence is DNA (paragraph 108).

Regarding claim 24, Straus teaches that a labeled target nucleotide sequence is obtained (Fig. 5, paragraphs 211 and 228).

Regarding claim 26, Straus teaches a target control sequence, i.e., another nucleotide sequence is complementary to the positive control probe on the chip (paragraph 210).

Regarding claim 41, Straus teaches that the positive control probe on the chip hybridizes to a target control sequence (Fig. 5, paragraphs 191, 210, 215) thus teaching positive control probe is complementary to a portion of target nucleotide sequence, which also meets the definition of the positive control probe as defined in the instant specification (paragraph 0027, as per USPGPUB). Straus also teaches that control nucleotide sequence is mixed with the biological sample and amplified synchronically with the target nucleotide sequence (paragraph 210).

Regarding claim 43, Straus teaches a method for genomic profiling, which includes a family of "tag sequences", which are used for detecting sequences in biological sample (paragraph 77). Straus also teaches these sequences are used to

dissect the individual SNP allele in a family of genes (paragraphs 77-79), which meets the definition of hybridization control probe as defined in the instant specification (paragraph 0028, as per USPGPUB), because they assess over all hybridization efficacy among family of genes. Straus also teaches that "tag sequence "are non-biological sequences, i.e., artificial synthetic sequences and detection array contains congruent tag sequence probe for detecting individual "tag sequences" (paragraphs 77-79) thus teaching the hybridization control probe complementary to synthetic nucleotide sequences not related to target genes.

Regarding claim 49, Straus teaches that hybridization reaction is conducted in a hybridization solution comprising sodium chloride, EPPS and sodium dodecyl sulfate, i.e., surfactant (paragraph 307).

Regarding claim 53, Straus teaches that the hybridization reaction is conducted at a temperature of 50 C, which is about 42 -70C (paragraph 307).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-2 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5, 567,809 issued Oct. 22, 1996) in view of Patterson et al (USPN 5,843,640 issued Dec. 1998).

Claims 2 and 7 are dependent from claim 1. Teachings of Apple et al regarding claim 1 are described previously in this office action.

Regarding claims 2 and 3, Apple et al teaches target nucleic acids are obtained from human bladder tissues and cell lines (Example 7, columns 41 and 42, lines 22-30 and 46-54) and does not teach specifically the target cell is leukocyte (claim 2) and is isolated using magnetic microbead (claim 7). However method of using magnetic microbead to isolate the cells including leukocytes and HLA target gene was known in the art at the time of the invention was made as taught by Patterson et al, who teaches the isolation of lymphocytes from PBMCs using magnetic beads and further teaches that the magnetic bead method provides highly enriched population of CD4 lymphocytes, i. e., leukocytes (column 12, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the target cell isolation method of Apple et al and use the magnetic bead method of Patterson et al with the expected benefit of obtaining highly enriched population of leukocytes from PBMCs as taught by Patterson et al (column 12, lines 46-50) thus having additional sources of cells for the HLA Typing method of Apple et al.

14. Claims 1 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5, 567,809 issued Oct. 22, 1996) in view of Straus (USPGPUB NO. 2002/0086289 published July 4, 2002).

Claim 41is dependent from claim 1. Teachings of Apple et al regarding claim 1 are described previously in this office action.

Regarding claim 41, Apple et al teaches contains a control probe that detects all of the HLA alleles (columns 53, 54 and 56, lines 50-67, 15-30 and 33-41). The control probe of Apple et al is the positive control probe as defined in the instant specification (paragraph 0027) and also because it detects all of the DRB alleles (column 56, lines 33-41). Apple et al do not teach the complementarity of positive control probe to a portion of the target nucleotide sequence. However, positive control probe complementary to a portion of the target nucleotide sequence was known in the art at the time of the invention was made as taught by Straus, who teaches a method for genomic profiling, which includes a positive control probe on the chip hybridizes to a target control sequence (paragraphs 191 and 210), which meets the definition of the

positive control probe as defined in the instant specification (paragraph 0027, as per USPGPUB). Straus also teaches adding positive control DNA sample to the experimental DNA sample for amplification thus teaching nucleotide sequence amplified synchronically with the experimental sample and further teaches that positive control probes are detected in all assays except for failure of assay steps (paragraph 0210). Straus further teaches failure to detect a signal from positive control probe indicates a false negative result (paragraph 0210).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the target detection method of Apple et al and include the positive control probe complementary to a portion of target sequence of Straus with the expected benefit of confirming the false negative result due to failure to detect a signal from positive control probe as taught by Straus (paragraph 0210).

15. Claims 1 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Straus (USPGPUB NO. 2002/0086289 published July 4, 2002) in view of Delenstarr et al (USPGPUBNO. 2002/0051973 published May 2, 2002).

Claim 42 is dependent from claim 41, which is dependent from claim 1. Teachings of Straus regarding claim 1 and 41 are described previously in this office action.

Regarding claim 42, Straus teaches a negative control probe (paragraph 180) but do not teach negative control probe has about 1-3 base pair mismatches compared to positive control probe. However, negative control probe having about 1-3 base pair

mismatches compared to positive control probe was in the art at the time of the invention was made as taught by Delenstarr, who teaches a positive control probe (paragraph 0076) and a negative control probe (paragraph 0075). Delenstarr also teaches that negative control probe (paragraphs 151-152, Table 5, SEQ ID NO. 32) has about 3 base pair mismatches when compared to the positive control probe (paragraph 0129, SEQ ID NO. 2). Delenstarr also teaches a method to identify the shortest length of background probes, i.e., negative control probe (Delenstarr et al also refers negative control probe as background probes, paragraph 0075) that mimics the properties of longer probes, yet have reduced affinities for complementary target sequence (paragraph 150).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the negative control probe of Straus for the genomic profiling and include shorter negative control probe of Delenstarr et al with the expected benefit of using a negative control probe of shorter length that mimics longer probe properties , yet having reduced affinity complementary target sequence as taught by Delenstarr et al (paragraph 150), thus reducing the cost of synthesizing negative control probe in the genomic profiling method of Straus.

16. Claims 1 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5, 567,809 issued Oct. 22, 1996) in view of Samartziduo et al (Life science news, 2001, 8, 1-3).

Claim 43 is dependent from claim 1. Teachings of Apple et al regarding claim 1 are described previously in this office action.

Regarding claim 43, Apple et al do not teach hybridization control probe is complementary to a synthetic nucleotide sequence not related to the target gene. However, hybridization control probe is complementary to a synthetic nucleotide sequence not related to the target gene was known in the art before the invention was made as taught by Samartziduo et al, who teaches microarray scorecard controls on the chip that includes positive, negative hybridization control probes and probes for dynamic range and ratio controls (Fig. 1, # 2, pg. 1, column 2, paragraph 3) and further teaches that these controls are YIR artificial genes and do not hybridize to human or mouse genes and the they are added as controls for hybridization (Table 1, pg. 1, column 2, paragraphs 3 and 4). Samartziduo et al further teaches that hybridization controls make a powerful tool for validation of microarray experiments, allowing assessment of target attachment, hybridization uniformity, detection limits, dynamic range and expression ratio (pg. 2, column 1, paragraph 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA typing method of Apple et al and include the hybridization control probe of Samartziduo et al with the expected benefit of using a better controls for validation of microarray experiments, allowing assessment of target attachment, hybridization uniformity, detection limits, dynamic range and expression ratio as taught by Samartziduo et al (pg. 2, column 1, paragraph 1) thus having additional control in the HLA typing method of Apple et al.

17. Claims 1, 46 and 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5, 567,809 issued Oct. 22, 1996) in view of Trau et al (Anal. Chem. 2002, 74, 3168-3173).

Claims 46 and 57-60 are dependent from claim 1. Teachings of Apple et al regarding claim 1 are described previously in this office action.

Regarding claims 46 and 57 Apple et al do not teach the immobilization control probe and assessing the efficiency of immobilization probe. However, the immobilization control probe and assessing the efficiency of immobilization probe was known in the art at the time of the invention was made as taught by Trau et al, who teaches an immobilization control probe on the chip (pg. 3169, column 2, paragraph 3, Table 1, Fig. 4 A-D, lane 7) and further teaches that the immobilization control probe is chemically modified at the 5' end (Table 1) and the other end of the immobilization control probe has a detectable Texas red label (Table 1, limitation of claim 46). Trau et al further teaches that the immobilization efficiency is assessed by analyzing a signal from the immobilization control probe (pg. 3171, column 2, paragraph 2, Fig. 4, see the legend for details, limitation of claim 57). Trau et al further teaches improving quantitative microarray data by normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization (pg. 3173, column 1, paragraph 1)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA typing and data analysis of Apple et al and to include additional immobilization control probe and hybridization analysis method of

Trau et al with the expected benefit of improving quantitative microarray data by normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization as taught by Trau et al (pg. 3173, column 1, paragraph 1) thus improving the HLA typing method of Apple et al.

Regarding claims 58-60, Apple et al teaches positive control probe, which detects all of the DRB alleles and further teaches the positive control probe provides guidance to score individual DRB allele either positive or negative based on the intensity of the spot relative to the positive control probe (column 56, lines 33-41) thus teaching criteria for hybridization specificity for the closely related HLA DRB probes on the chip (columns 53 and 54, lines 50-67 and 15-30, limitation of claim 60). Apple et al do not teach labeled synthetic probe (claim 58) and the ratio between the hybridization signal involving the positive hybridization control probe and the hybridization signal involving the negative hybridization control probe (claim 59) and criteria for determining the positive signals (claim 60). However determining the ratio of signal intensities and establishing criteria for the positive signal for the closely related probes were known in the art at the time of the invention was made as taught by Trau et al, who teaches an array of closely related genes from medicinal plants (pg. 3170, column 2, paragraph 2) and teaches explicitly probes for five different genes (PP, DI, AM, TG and HF) and an immobilization control (Fig. 4, Table 1). Since there is no limiting definition for synthetic nucleotide sequence, the immobilization control probe, which is labeled, is the synthetic nucleotide probe (Trau et al, Table 1) and the probe for PP gene is the hybridization

control probe. Trau et al also teaches the analysis of the hybridization of the immobilization control probe and the PP probe (Fig. 4A, limitation of claim 58) thus providing the assessment of hybridization efficiency between hybridization control probe and the synthetic nucleotide.

Trau et al further teaches the hybridization of PP sample to PP probe (Fig. 4A, column 2) and AM probe (Fig. 4A, column 3), which is a negative control probe, and meets the requirement as defined in the instant specification (Instant specification, paragraph 0027 as per PGPUB) because it comprises multiple base pair changes compared to PP probe (Table 1). Trau et al teaches the ratio of hybridization signal (specific hybridization, Fig. 4A, column 2) to noise (background, Fig. 4A, columns 1 and 8 no probes) is greater than 150 compared to the ratio of hybridization signal (specific hybridization) to noise (unspecific hybridization with AM probe in Fig. 4A, column 3) is greater than 80 (pg, 3172, column 1, paragraph 1) thus teaching the increased ratio between the hybridization signal involving the positive hybridization control probe and the hybridization signal involving the negative hybridization control probe (limitation of claim 59).

Trau et al also teaches an embodiment, wherein the ratio of hybridization signal (specific hybridization, Fig. 4B, column 6) to noise (background, Fig. 4A, columns 1 and 8 no probes) is greater than 150 (pg, 3172, column 1, paragraph 1, limitation of claim 60, step 'a') and further teaches the signal to noise ratio range from 150 to 4 (Fig. 4C, column 6) to 2 (Fig. 4D, column 6) thus teaching a range of the ratio of hybridization signal (pg, 3172, column 1, paragraph 1, limitation of claim 60, step 'b') and further

teaches comparing the hybridization signal of all probes giving positive signals (Fig. 4A, limitation of claim 60, step 'c') and two positive signals (probe PP and DI) of closely related genes (Fig. 4 A and B, limitation of claim 60, step 'd'). Trau et al also teaches further improvement in quantifying microarray data at a signal to noise ratio of 2, by adjusting template concentration for hybridization and normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization (Fig. 5, pgs. 3172 and 3173, column 1, paragraph 1)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the array preparation and data analysis of Apple et al and to include additional immobilization control probe and hybridization analysis method of Trau et al with the expected benefit of improving quantifying microarray data at a signal to noise ratio of 2, by adjusting template concentration for hybridization and normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization as taught by Trau et al (Fig. 5, pgs. 3172 and 3173, column 1, paragraph 1) thus improving the DRB typing by array method of Apple et al.

18. Claims 1 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5, 567,809 issued Oct. 22, 1996) in view of Samartziduo et al (Life science news, 2001, 8, 1-3) and further in view of Trau et al (Anal. Chem. 2002, 74, 3168-3173).

Claim 47 is dependent from claim 1. Teachings of Apple et al regarding claim 1 are described previously in this office action.

Regarding claim 47, Apple et al teaches contains a control probe that detects all of the HLA alleles (columns 53, 54 and 56, lines 50-67, 15-30 and 33-41). The control probe of Apple et al is the positive control probe as defined in the instant specification (paragraph 0027) and also because it detects all of the DRB alleles (column 56, lines 33-41). Apple et al do not teach a negative control probe, a hybridization control probe and an immobilization control probe. However, a negative control probe, a hybridization control probe was known in the art before the invention was made as taught by Samartziduo et al, who teaches microarray scorecard controls on the chip that includes positive, negative hybridization control probes and probes for dynamic range and ratio controls (Fig. 1, # 2, pg. 1, column 2, paragraph 3) and further teaches that these controls are YIR artificial genes and do not hybridize to human or mouse genes and the they are added as controls for hybridization (Table 1, pg. 1, column 2, paragraphs 3 and 4). Samartziduo et al further teaches that hybridization controls make a powerful tool for validation of microarray experiments, allowing assessment of target attachment, hybridization uniformity, detection limits, dynamic range and expression ratio (pg. 2, column 1, paragraph 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA typing method of Apple et al and include the hybridization control probe of Samartziduo et al with the expected benefit of using a better controls for validation of microarray experiments, allowing assessment of target

attachment, hybridization uniformity, detection limits, dynamic range and expression ratio as taught by Samartziduo et al (pg. 2, column 1, paragraph 1) thus having additional control in the HLA typing method of Apple et al.

Apple et al in view of Samartziduo et al do not teach an immobilization control probe. However, an immobilization control probe was known in the art at the time of the invention was made as taught by Trau et al, who teaches an immobilization control probe on the chip (pg. 3169, column 2, paragraph 3, Table 1, Fig. 4 A-D, lane 7). Trau et al further teaches improving quantitative microarray data by normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization (pg. 3173, column 1, paragraph 1)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA typing and data analysis of Apple et al in view of Samartziduo et al and to include additional immobilization control probe and hybridization analysis method of Trau et al with the expected benefit of improving quantitative microarray data by normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization as taught by Trau et al (pg. 3173, column 1, paragraph 1) thus improving the HLA typing method of Apple et al in view of Samartziduo et al.

Conclusions

19. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571)-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Narayan K. Bhat, Ph. D.

Examiner

Art Unit 1634

BJ FORMAN, PH.D.
PRIMARY EXAMINER